REMARKS

Status of the Claims

Claims 32-62 are pending in the present application. Claims 33-62 were substantively examined and are rejected as being allegedly obvious under 35 U.S.C. §103(a). Claims 32-62 are rejected under 35 U.S.C. §103(a) as being unpatentable for the reasons set forth in the Official Action mailed 5/30/01, in the rejection of claims 1-3, 6-11, 13-26, and 28-30 under 35 U.S.C. §103(a) over Meade, *et al.* in view of Manoharan, *et al.* and Gold, *et al.* for the reasons of record set forth in the official action mailed 2/07/02.

Claims 32-61 are rejected under 35 U.S.C. §103(a) as being unpatentable over Nazarenko, *et al.* (U.S. 5,866,336) in view of Templeton, *et al.* (*Nature Biotechnology*, **15**:647-652, 1997) for reasons of record in the Official Action mailed 2/07/02.

Claim 32 is amended. The Markush grouping of generic structures is replaced by a single structure that is analogous to the structure found in claim 50. Species of substituents found in claim 50 are amended to their generic counterparts, which were recited in claim 32. For example, CHOL is replaced by stabilizing moiety. The specification describes CHOL as an exemplary stabilizing moiety. Thus, one of skill would immediately appreciate that CHOL and stabilizing moiety were interchangeable in the structure of claim 50. Moreover, the donor and acceptor ("quencher") of "light energy" of claim 50 are amended to donor and acceptor of "molecular energy." One of skill would immediately recognize that "light energy" and "molecular energy" are interchangeable. The groups "Nu^1," Nu^2, and R^1-R^4 are added. The group "A" is amended to "NA."

Claim 50 is amended to simplify awkward syntax. The meaning of the amended language is identical to that in earlier versions of claim 50.

No new matter is added by the amendments.

The Invention

The pending claims set forth an embodiment of the Applicant's invention, which is a novel nucleic acid probe. The probe includes unique structural features that are neither disclosed nor suggested by the art presently of record.

The probe is conveniently conceptualized as including three subunits:

(1) a central nucleic acid "core," designated "NA";

(2) an energy donor-stabilizing moiety region; and

(3) an energy acceptor-stabilizing moiety region.

The nucleic acid "core" recognizes and hybridizes to a complementary nucleic acid.

The "energy donor-stabilizing moiety" region includes five components:

(1) a first linker moiety ("R^2") that is bound through a phosphodiester linkage to a terminal nucleic acid residue of the "core";

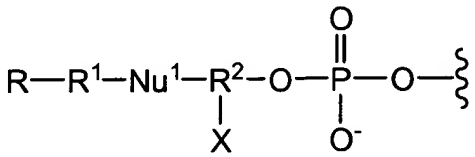
(2) a stabilizing moiety ("X") that is attached to the first linker moiety;

(3) a nucleic acid residue ("Nu^1"), outside the "core," which is attached to the first linker moiety;

(4) a second linker moiety ("R^1") that is attached to the nucleic acid residue of (3); and

(5) an energy donor moiety ("R") that is attached to the second linker moiety.

The "energy donor-stabilizing moiety" region has the structure:



Thus, the linker moiety R^2 links together two nucleic acids (the second nucleic acid is "NA," attached to the open valence of the oxygen in the structure above, forming a phosphodiester linkage) and a stabilizing moiety. The linker moiety R^1 links together a

nucleic acid and an energy donor moiety. As presently claimed, the "energy donor-stabilizing moiety" region is appended to a terminal nucleic acid of the "core" through a phosphodiester linkage.

The "energy acceptor-stabilizing moiety" region also includes five components:

(1) a first linker moiety ("R^3") that is bound through a phosphodiester linkage to a terminal nucleic acid residue of the "core," other than that to which the energy donor-stabilizing moiety region is attached;

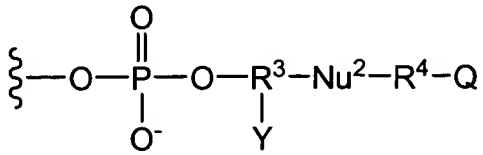
(2) a stabilizing moiety ("Y") that is attached to the first linker moiety;

(3) a nucleic acid residue ("Nu^2"), outside the "core," which is attached to the first linker moiety;

(4) a second linker moiety ("R^4") that is attached to the nucleic acid residue of (3); and

(5) an energy acceptor moiety (Q") that is attached to the second linker moiety.

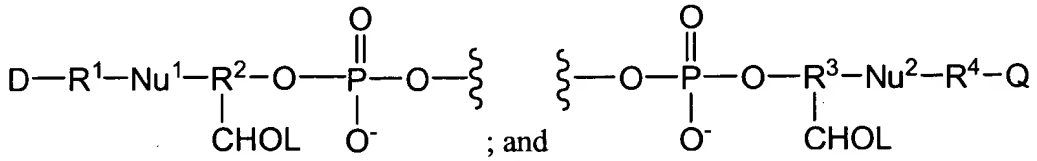
The energy acceptor-stabilizing moiety subunit has the formula:



Thus, the linker moiety R^3 links together two nucleic acids (the second nucleic acid is "NA," attached to the open valence of the oxygen in the structure above, forming a phosphodiester linkage) and a stabilizing moiety. The linker moiety R^4 links together a nucleic acid and a quencher. As presently claimed, the "energy donor-stabilizing moiety" region is appended to a terminal nucleic acid of the "core" through a phosphodiester linkage.

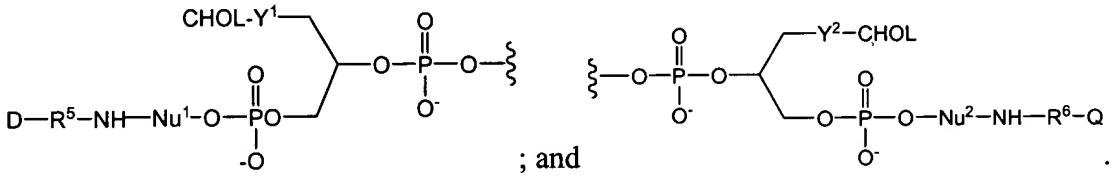
The two subunits detailed above are joined by a nucleic acid sequence "NA". Thus, claim 32 explicitly sets forth the configuration of the three distinct regions of the probe and their positional relationship to each other.

The pending claims set forth exemplary embodiments of the invention with progressively more detail regarding the molecular structure of the probe. For example, claim 50 sets forth a probe that includes the subunits:



attached to the central nucleic acid core "NA".

Claim 57 includes even greater structural detail for the probes, displaying the structure of an exemplary tri-functional linker arm that joins the stabilizing moiety and the nucleic acid-linker-donor (acceptor) moiety to the NA core through a phosphodiester linkage:



In operation, the stabilizing moieties interact to bring the energy donor and energy acceptor of the unhybridized probe into operative proximity such that energy is transferred from the donor to the acceptor.

The Rejections

Previous Office Actions, have asserted that Applicant's invention is obvious over certain combinations of references. The Actions state that the Applicant has not set forth sufficient reason why the compound arising from the combination of the references would not have the ***properties*** claimed by Applicant. It is respectfully submitted that the Examiner has focused on the operational property of the instant probes and has not ***examined the structures*** explicitly set forth in the claims. Applicant has reached this conclusion based upon the absence in the Actions of an explicitly stated

rationale for the alleged chemical ***structural*** obviousness of the instantly claimed compounds.

Applicant respectfully asserts the chemical structural elements recited in claims 50 and 57 and their dependents were not accorded the proper weight during examination. As discussed below, claims 50 and 57 and their dependents explicitly recite structural features that are neither disclosed nor suggested by any of the references now of record in the present application, nor does their combination suggest the claimed compounds. Certain of these elements are now also explicitly recited in claim 32 and its dependents. Accordingly, in this Request for Further Examination, the applicant respectfully requests that the ***explicitly claimed structures be searched and examined*** in a manner consistent with the examination of any claimed chemical structure.

To form the basis of a *prima facie* case of obviousness, the prior art must disclose or suggest more than just the isolated elements of Applicant's claimed compounds. In particular, the prior art must suggest arranging the isolated elements in the manner in which they are explicitly set forth in Applicant's claims. Furthermore, the prior art must disclose or suggest that it is advantageous to combine the isolated elements in the manner that the applicant has combined them. For example, in the present application, the prior art should minimally disclose or suggest subunits of the compounds such as the "energy donor-stabilizing moiety subunit" and the "energy acceptor-stabilizing moiety subunit" attached to antipodal termini of the "core" nucleic acid. Finally, the prior art must provide one of skill with a reasonable expectation of success that the claimed invention could be assembled from the isolated elements utilizing the teachings of the cited references.

The earlier Actions have not specifically addressed why claims 50 and 57 and their dependents are deemed to be unpatentably obvious over the combined references, despite the structural details found in these claims, none of which is disclosed or suggested by the art of record. Thus, it is impractical for the Applicant to address directly the Examiner's concerns. Should the Examiner wish to maintain the present rejection, or advance a new rejection, the Applicant respectfully requests that the

Examiner, in accordance with 35 USC § 132, set forth the specific reasons why each claim is rejected:

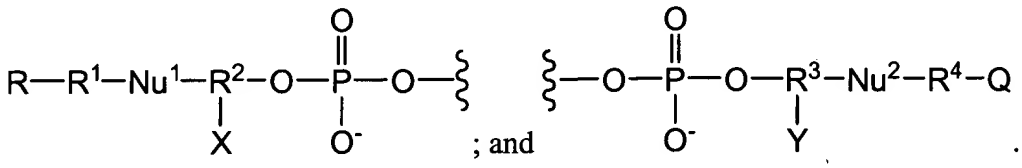
> [w]henever, on examination, any claim for a patent is rejected, . . . the Commissioner shall notify the applicant thereof, stating the reasons for such rejection . . . ."

Thus, the applicant respectfully requests the Examiner to identify where each element of the claimed compounds is found in the prior art for ***all*** of the pending claims. Moreover, the Applicant requests that the Examiner identify precisely where in the prior art the specific configuration of elements claimed by the Applicant is disclosed or suggested.

Over Meade et al. ("Meade") in view of Manoharan et al. ("Manoharan") and Gold et al. ("Gold")

The present Action rejects claims 32-62 under 35 U.S.C. §103(a) as being unpatentable for the reasons set forth in the Official Action mailed 5/30/01, in the rejection of claims 1-3, 6-11, 13-26, and 28-30 under 35 U.S.C. §103(a) over Meade, *et al.* in view of Manoharan, *et al.* and Gold, *et al.* for the reasons of record set forth in the official action mailed 2/07/02. Applicant responds to the rejection with amendment and traverse.

For a *prima facie* case of obviousness to be properly made out, one or more of the cited references must disclose or suggest ***chemical structures corresponding to the subunits*** set forth above under the heading "The Invention." Minimally, the references must disclose or suggest a probe that includes subunits having the formula:



Applicant submits that the references of record are deficient in their failure to disclose or suggest a probe or other compound that includes the subunits set forth above or the corresponding subunits set forth in claims 50, 57 and their dependents.

Meade

Meade discloses nucleic acid probes that include an energy donor and an energy acceptor moiety ("D/A moieties"). Each D/A moiety is attached to the nucleic acid through ***a nitrogen atom***. In one embodiment, the D/A moieties of Meade are attached to the amine moiety of an amino-ribose (*see*, **FIG. 3**). In another embodiment, the D/A moieties are bound to the nucleic acid through a ***phosphoramide linkage*** (*see*, **FIG. 5**). Thus, Meade fails to disclose or suggest a nucleic acid that is derivatized with a linker arm through a phosphodiester bond such as is claimed by the Applicant.

Moreover, Meade neither discloses nor suggests combining nucleic acid-bound D/A moieties with a nucleic acid-bound stabilizing moiety. Thus, Meade cannot be interpreted to suggest a nucleic acid probe in which a linker moiety joins two nucleic acids and a stabilizing moiety. Furthermore, Meade cannot be said to disclose nor to suggest a nucleic acid probe having two stabilizing moieties attached thereto. Thus, Meade does not disclose a nucleic acid probe having an "energy donor-stabilizing moiety subunit" or "energy acceptor-stabilizing moiety subunit".

Manoharan

Manoharan sets forth a nucleic acid that can have one or more cholic acid (or other lipophilic) moiety bound thereto. The reference discloses:

> Cholic acid can be attached to ***both ends*** of a linked nucleoside sequence by reacting the 3', 5'-diamino sequence with the cholic acid active ester...in even further embodiments...an oligonucleoside sequence bearing an aminolinker at the ***2'-position*** of one or more selected nucleosides is prepared using a suitably functionalized nucleoside. See, column 8, lines 45-56.

Thus, Manoharan discloses attaching cholic acid derivatives to ***amine-containing linkers*** attached to the 3', 5, or 2' hydroxyls of a nucleic acid. Nothing in the Manoharan disclosure suggests Applicant's instantly claimed structures.

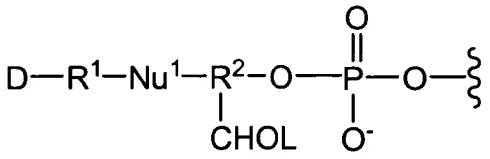
In contrast to Manoharan, Applicants claim compounds in which the linker arm bearing the stabilizing moieties (e.g., cholic acid derivatives) are attached to ***internucleotide phosphodiester bridges***, not to the 3'-, 5'-hydroxyls of the terminal nucleotides, nor the 2'-hydroxyl of an internal nucleotide. Moreover, Applicant's compounds include a linker arm that attaches two nucleic acids and a stabilizing moiety, such as that set forth in each of Applicant's claims; nothing in Manoharan suggests the use of the claimed linker arm.

Moreover, Manoharan fails to suggest a nucleic acid probe that includes two cholic acid moieties and an energy donor moiety and an energy acceptor moiety.

Gold

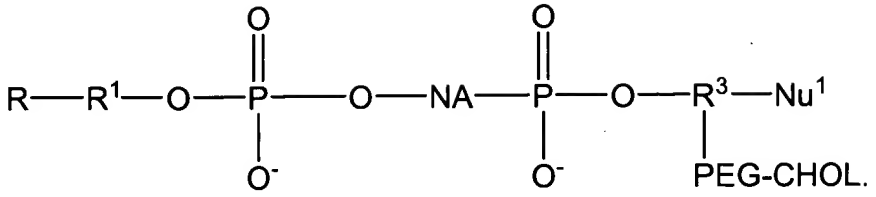
Gold discloses a number of nucleic acid conjugates, some of which include a fluorescent moiety and a lipophilic moiety. The Examiner has focused on the nucleic acid set forth in **FIG. 1B** of Gold. The nucleic acid set forth in **FIG. 1B** includes fluorescein at one terminus of the nucleic acid and a linker arm bearing a cholesterol-PEG derivative at the penultimate position at the ***opposite terminus*** of the nucleic acid chain.

The Gold nucleic acids are missing each of Applicant's claimed substructures set forth above, e.g.,

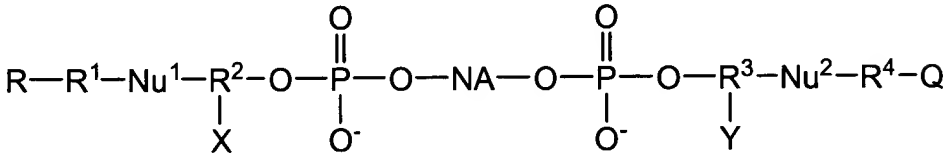


in which R is an energy donor, R^1 is a non-nucleotide linker Nu^1 is a nucleic acid residue, R^2 is a non-nucleotide linker and X is a stabilizing moiety.

For example, translating the structure of Gold's **Fig. 1B** into Applicant's claim language, the Gold nucleic acid has the structure:



When contrasted with Applicant's claimed structure, the differences between the two structures are apparent:



The linker-stabilizing moiety (R^2-X) is missing from the left side of the Gold nucleic acid. Moreover, the linker-energy acceptor moiety (R^4-Q) is missing from the right side of the Gold nucleic acid. Thus, the Gold nucleic acid does not include an "energy donor-stabilizing moiety" subunit nor does it have an "energy acceptor-stabilizing moiety" subunit.

As set forth above, the combination of Meade, Manoharan and Gold fails to disclose or suggest each element of Applicant's claimed invention. In particular, the references cannot be said to disclose or suggest a nucleic acid probe having an "energy donor-stabilizing moiety subunit" and "energy acceptor-stabilizing moiety subunit" as is presently claimed.

Furthermore, there is no motivation to combine the references to produce Applicant's claimed compounds. The claimed structures were designed to fulfill a specific function. The stabilizing moieties interact when the probe is non-hybridized, thereby bringing the donor and the acceptor into operative contact and quenching fluorescence from the donor. When hybridized, the interaction between the stabilizing moieties is disrupted, the donor and acceptor move out of operative contact and the probe generates fluorescence. The arrangement of the first stabilizing moiety and the donor and the second stabilizing moiety and the acceptor in the claimed structure enhances the interaction between the donor and the acceptor. As there is no disclosure nor suggestion in the art that two stabilizing moieties would interact to bring a donor and quencher into

operative contact, one of skill would not have been motivated to assemble the presently claimed structures.

Moreover, in view of the state of the art, the proposed combination of references would not have provided one of skill with a reasonable expectation of success. The art fails to disclose or suggest each claimed structural element of the applicant's compounds. The art is silent with regard to the ability of two stabilizing moieties to bring a donor and an acceptor moiety into operative contact. Thus, there could have been no reasonable expectation of success.

Over Nazarenko in view of Templeton

The present Action maintains the rejection of claims 32-61 as being allegedly obvious over Nazarneko in view of Templeton for the reasons set forth in the Action of February 7, 2002. Applicant responds with amendment and traverse.

The Examiner states that Nazarenko teaches probes in which the nucleic acid self-hybridizes to bring the donor and acceptor into operative contact, admitting that the reference fails to disclose the interaction of two non-nucleic acid stabilizing moieties to induce this contact. The Action asserts that "non-nucleic acid moieties and in particular hydrocarbons and steroids were known in the art to stabilize structure of nucleic acid compounds." The asserted knowledge apparently is based upon a statement found in Templeton "[h]igh cholesterol content is known to ***increase the stability of liposomes***." Increasing the stability of liposomes, however, completely unrelated to "stabilizing" a particular conformation of a nucleic acid probe, i.e., one in which the donor and acceptor are in operative proximity. Liposomes are macromolecular assemblies of a plurality of ***intermolecularly associated*** monomers. In contrast, the claimed compounds are single nucleic acid probes having distinct regions that react ***intramolecularly***.

Applicant's claims explicitly recite that the stabilizing moieties are "non-nucleic acid stabilizing moieties." In contrast, Nazarenko's probes rely on nucleic acid self-hybridization. Nazarenko is silent with regard to a nucleic acid probe in which two

non-nucleic acid stabilizing moieties interact to bring the donor and acceptor into operative proximity.

The deficiency of Nazarenko is not remedied by Templeton, which discloses that cholesterol-derivatized nucleic acids ***stabilize liposomes*** containing the cholesterol-nucleic acids. Templeton is silent regarding a probe that combines a nucleic acid conformation "stabilizing moiety" with a donor and an acceptor moiety.

In view of the above, the combination of Nazarenko and Templeton cannot be said to disclose or suggest Applicant's claimed compounds. Neither of the references suggests the specific structures claimed. Moreover, the combination of the references fails to suggest a nucleic acid probe in which two or more stabilizing moieties is combined with a donor and an acceptor moiety. Accordingly, Applicant respectfully requests the withdrawal of the reference of claims 32-61.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is urged. If the Examiner believes a telephone conference would aid in the prosecution of this case in any way, please call the undersigned at 415-576-0200.

Respectfully submitted,

Jeffry S. Mann, Ph.D.
Reg. No. 42,837

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, 8th Floor
San Francisco, California 94111-3834
Tel: 415-576-0200
Fax: 415-576-0300
JSM:kad
11453283 v1